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Urinary Excretion of Methylated Catecholamine Metabolites in a Child With Neuroblastoma Maturing Into Ganglioneuroma

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Neuroblastomas are malignant tumors derived embryonically from the neural crest. Biological diagnosis relies on assay of urinary excretion of homovanillic acid (HVA), vanillylmandelic acid (VMA), and dopamine (DA). Spontaneous regression of these neoplasms has been reported by numerous investigators. The authors report the case of a child with neuroblastoma that illustrates the relationship between catecholamine metabolites and tumor maturation. At 1 month of age, this infant presented an adrenal neuroblastoma with multiple metastases (stage IV); the initial histological diagnosis based on examination of cutaneous metastases was neuroblastoma. At the age of 6 months, after chemotherapy, the primary tumor was resected; hepatic metastases were discovered at laparotomy. The histological diagnosis for all lesions was highly differentiated, mature ganglioneuroma-like tissue. The main biochemical abnormality at the time of diagnosis was an elevation in normetanephrine (NMN). HVA was only slightly increased but rose progressively during chemotherapy; it dropped back to normal levels after the sixth course. This case illustrates the potential benefits of separate assays of urinary methylated catecholamine metabolites for biochemical diagnosis and therapeutic management of neuroblastoma in addition to assays of HVA, VMA, and DA. Case findings suggest existence of a transformation process with maturation of the tumor involving enzymatic regulation and expression of MAO.

Key words: neuroblastoma, ganglioneuroma, maturation, monoamine oxidase, catecholamine metabolites

INTRODUCTION

Neuroblastomas are malignant tumors derived embryonically from the neural crest that can arise in any site containing autonomic nervous system fibers. Biological diagnosis relies on assay of urinary excretion of homovanillic acid (HVA), vanillylmandelic acid (VMA), and dopamine (DA); HVA is the main DA metabolite while VMA is the main noradrenaline (NA) and adrenaline (A) metabolite (Fig. 1). The prognosis depends on the disease stage and patient age. Stage I and IIa tumors diagnosed before the age of 1 year have a favorable prognosis whereas long-term survival is only 20% for stage IV tumors diagnosed after 2 years of age. However, there are reports of regression (maturation) of stage IVS lesions into benign ganglioneuromas spontaneously [1–4] or in response to therapy [5–8]. We now describe the case of a patient with an adrenal neuroblastoma and metastases which excreted large amounts of urinary normetanephrine (NMN); HVA was only slightly increased, but paradoxically rose progressively during chemotherapy before dropping back to normal levels after the sixth course.

MATERIALS AND METHODS

The urinary methylated catecholamine metabolites normetanephrine (NMN), metanephrine (MN), and 3-methoxytyramine (3-MT) are useful for early diagnosis of pheochromocytomas, tumors that usually arise from the neural crest. Elevated excretion of these methylated metabolites may be isolated findings or may be associated with neuroblastoma [9].

Patient

At the age of 1 month, an infant born on March 1, 1992 was hospitalized for a neuroblastoma of the right adrenal gland with multiple cutaneous metastases and a lytic bone lesion in the left parietal area (neuroblastoma stage IV) [10]. Bone marrow smears revealed neuroblas-

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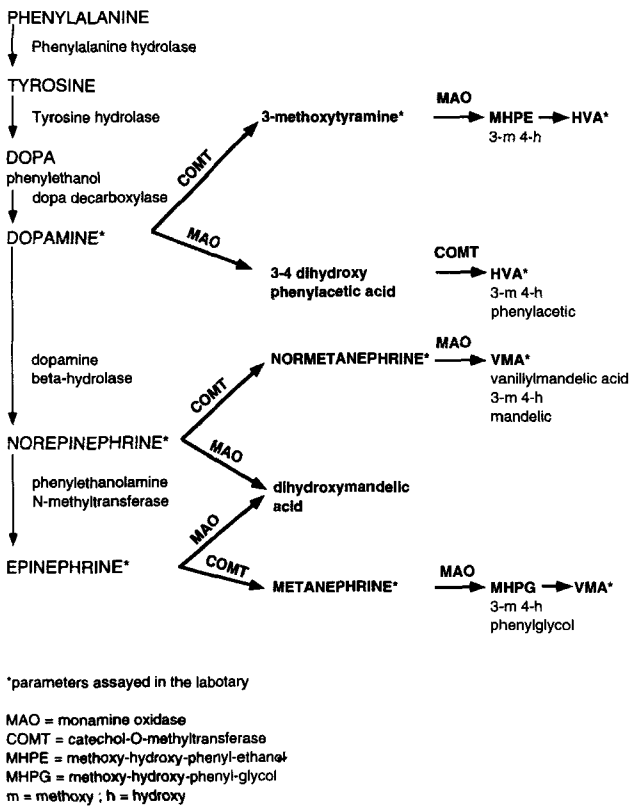


Fig. 1. Catecholamine synthesis and catabolism.

toma cells while metaiodobenzylguanidine (MIBG) radionuclide scanning demonstrated weak uptake in the tumor and chest wall metastasis.

Treatment consisted in four cycles of CADO (oncovin, endoxan, adriamycin) followed by two cycles of cisplatin and VP-16. On September 10, 1992, when the patient was 6 months of age, the primary tumor was resected; approximately 15 liver nodules under 1 cm diameter were discovered during surgery. Anatomopathologic examination revealed highly differentiated mature ganglioneuroma-like tissue in the nodes, hepatic metastases, and primary tumor. No n-myc amplification was detected in a cutaneous metastasis before chemotherapy or in the primary tumor after the cycles of CADO. Regular follow-up without complementary treatment was instituted.

A small right supramammary nodule resected in August 1993 and a progressive lytic lesion on the left chest wall resected in December 1993 corresponded to mature neuroblastoma. Surveillance without therapy was continued.

Measurement of Catecholamine Metabolites

Catecholamines and their methylated metabolites were assayed by HPLC with electrochemical detection [11,12]; HVA and VMA were determined by gas chromatography [13].

RESULTS

Results of the initial workup included: NA 160 nmol/24 hr (normal 27–116); A < 10 nmol/24 hr (normal 4–14); DA 1,200 nmol/24 hr (normal 220–1,780). VMA 20 μmol/24 hr (normal < 10), and HVA (22 μmol/24 hr; normal < 10) were both slightly increased; NMN was elevated (5.8 μmol/24 hr; normal 0.11–0.59). MN was very low (0.02 μmol/24 hr; normal 0.03–0.12) and 3-MT was increased (1.06 μmol/24 hr; normal 0.07–0.39).

Several days later, before the start of treatment, NMN had risen to 7.5 μmol/24 hr (normal × 12); 3-MT was still increased (1.2 μmol/24 hr = normal × 3). VMA and HVA were only moderately elevated (respectively, 22 and 27 μmol/24 hr).

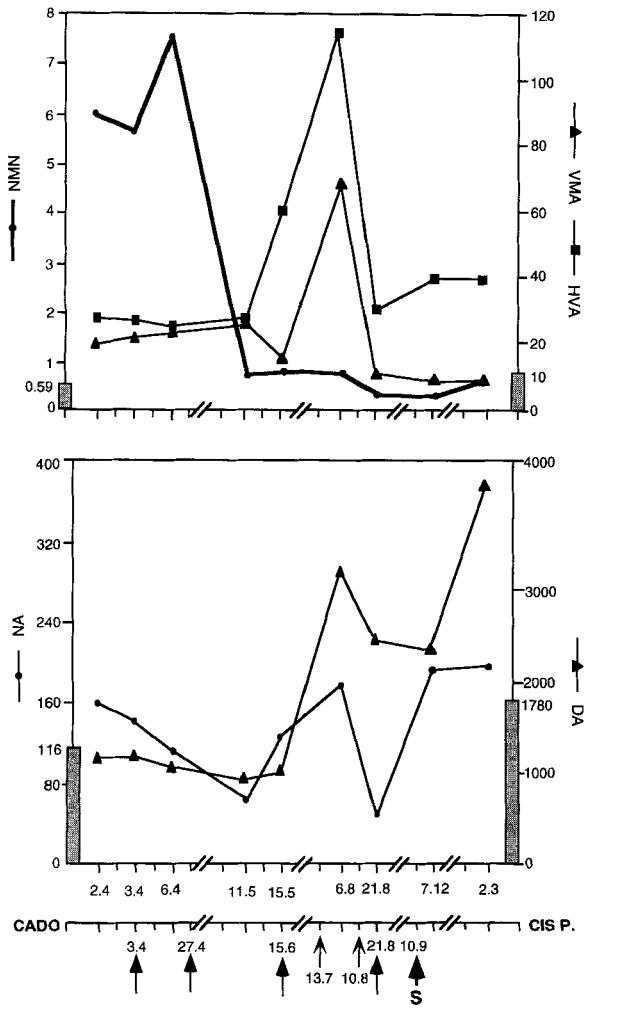
The tumoral syndrome regressed rapidly after two cycles of multiagent chemotherapy, at which time assays revealed: NA 63 nmol/24 hr; A 4 nmol/24 hr; DA 930 nmol/24 hr. NMN had decreased and was only slightly above normal (0.7 μmol/24 hr); 3-MT was only slightly increased (0.52 μmol/24 hr). Paradoxically, these findings were accompanied by a progressive rise in HVA, which reached 115 μmol/24 hr at 5 months of age when VMA was 69 μmol/24 hr. The HVA and VMA levels dropped after the 6th chemotherapy course to, respectively, 24 and 8 μmol/24 hr.

The main steps in urinary excretion of catecholamines and their derivatives are summarized in Figure 2.

DISCUSSION

Spontaneous remission of neuroblastoma has been reported on numerous occasions. Incomplete enzymatic equipment in the neuroblastoma is another classically described feature [14]. The monoamine oxidases A and B (MAO-A and MAO-B) are both detectable in extraneuronal cells (liver); MAO-A is present in the catecholaminergic neurons and is responsible for intraneuronal oxidative deamination, the predominant pathway of catecholamine catabolism. The catecholamine ortho-methyltransferase (COMT) is not found in neurons, but is present in the non-neuronal cells of tissues such as the liver, kidney, brain, and choroid plexus. In these cells, COMT is the preferential enzyme of catabolism and its products are partially deaminated or excreted as is.

At the time of the first hospitalization, the enzymatic equipment of our patient's tumor appeared to lack MAO because urinary excretion of VMA and HVA was only moderately raised, whereas later on, even during multidrug therapy, these values rose paradoxically; initial excretion of urinary methylated metabolites had, however, proved the existence of excessive tumoral catecholamine



NA Noradrenaline DA : Dopamine (nanomol/L)
NMN : Noramelanephrine VMA : Vanillylmandelic acid
HVA : Homovanilic acid (micromol/L)
Normal values are shadowed on the respectice axis :
Chimio therapy : CADO : oncovin - Endoxan - Adriamycin (3/4, 27/4, 15/6, 21/8, 1992)
CISP : Cis Platin (13/7, 10/8 1992)
S : Surgery

Fig. 2. The main steps in urinary excretion of catecholamines and their derivatives and dates of the treatments.

secretion. The tumor thus, perhaps, did not possess any MAO equipment (or had insufficient equipment) but acquired it secondarily, during spontaneous or treatment-induced tumoral "maturation." Prospective investigations of methylated catecholamines in very young infants would be helpful.

Findings at the time of diagnosis suggest that our patient's tumor was forming and secreting DA, a low percentage of which was metabolized to HVA. First of all, conversion of DA to NA by dopamine beta-hydroxylase (DBH) appeared to decrease after initiation of chemotherapy, and DBH activity could take place in the tumor. In addition, DA reaching the systemic circulation might be captured by the peripheral sympathetic neurons and converted to NA and its metabolites. If the initial effects of chemotherapy reduced DA conversion to NA, it would be expected that NA formation and metabolism would be diminished, whereas DA metabolite (HVA) formation might increase. With further regression of the tumor, HVA excretion would also decrease. Our findings support this hypothesis.

CONCLUSION

This case of neuroblastoma illustrates the benefits of separate assays of urinary methylated catecholamine metabolites for biochemical diagnosis and therapeutic management in addition to assays of HVA, VMA, and DA, because the individual values of each fraction reflect a particularity of tumoral evolution. Our findings suggest existence of a process involving enzymatic expression of MAO leading to maturation of certain neuroblastomas into ganglioneuromas.

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